Methacholine versus Mannitol Challenge in the Evaluation of Asthma

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Conflict of interest

- Dr Sandra Anderson is the Inventor on the patent that cover these applications for mannitol
- The patent is owned by her employer SSWAHS
- The rights to commercialise the intellectual property are licensed to Pharmaxis Ltd
- Dr Anderson purchased her own shares on the open market and holds no options.
- Dr Anderson is a consultant to Pharmaxis Ltd
- Dr Anderson receives a 10% share of the royalties paid to SSWAHS

Q: Why do we use bronchial provocation tests in the evaluation of Asthma ?

Performing the appropriate bronchial provocation test (BPT) by using either a direct or an indirect stimulus to identify bronchial hyperresponsiveness (BHR) reduces the possibility of over and under diagnosis of asthma based on history and symptoms.

Q: When do we need to know about bronchial hyperresponsivness ?

- Upon presentation of a person with symptoms suggestive of asthma but with normal lung function and doubt about the diagnosis of asthma

- In a person entering an occupation or recreational activity where BHR could be a potential problem

- In a person well-controlled on treatment for a long period in whom it may be useful to back titrate treatment e.g. the dose of steroid

- Following exposure to an occupational irritant or allergen that has induced symptoms of asthma

Q: Why do we need to know about bronchial hyperresponsiveness ?

- In a person with normal lung function BHR, to an indirectly acting stimulus, is an indirect index of the presence of airway inflammation.

- The inflammation of asthma involves eosinophils and mast cells

- The number of these cells & concentration of mediators of bronchoconstriction are reduced with treatment with inhaled steroids & BHR is concomitantly reduced

Q: What are the types of Bronchial Provocation Tests that are used to evaluate asthma ?

INDIRECT challenge test: e.g. mannitol

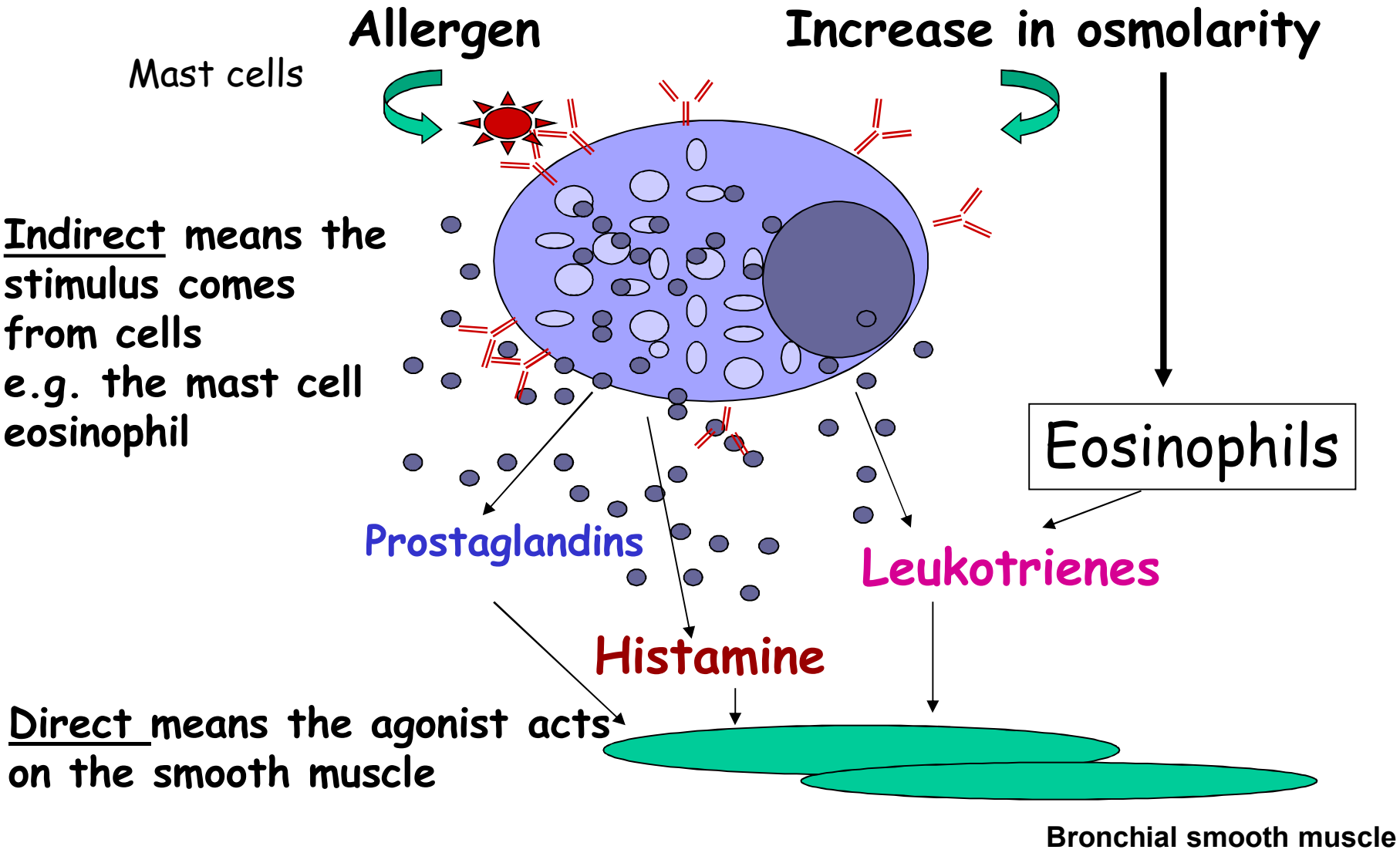
"Indirect challenges act by causing the release of endogenous mediators that cause the airway smooth muscle to contract, with or without effect in inducing microvascular leakage.

Joos GF et al. ERS Task Force. Eur Respir J 2003; 21:1050-68

DIRECT challenge test: e.g. methacholine

The agent is administered and acts on a specific receptor on the bronchial smooth muscle causing it to contract and the airways to narrow. Identifies bronchial responsiveness consistent with asthma or with airway injury or airway remodeling.

Q: What is the source of the mediators that cause Bronchial Smooth Muscle to contract ?



Why perform a bronchial provocation test ?

- ***Is it asthma ?***

  to exclude asthma ?

  one needs a sensitive test

  to confirm asthma ?

  one needs a specific test

- ***to manage asthma ?***

  one needs a test that correlates with the response of asthma to treatments

Is Methacholine a Rule Out test ?

- Methacholine challenge has been promoted for its clinical utility in excluding the diagnosis of asthma based on a negative test result.

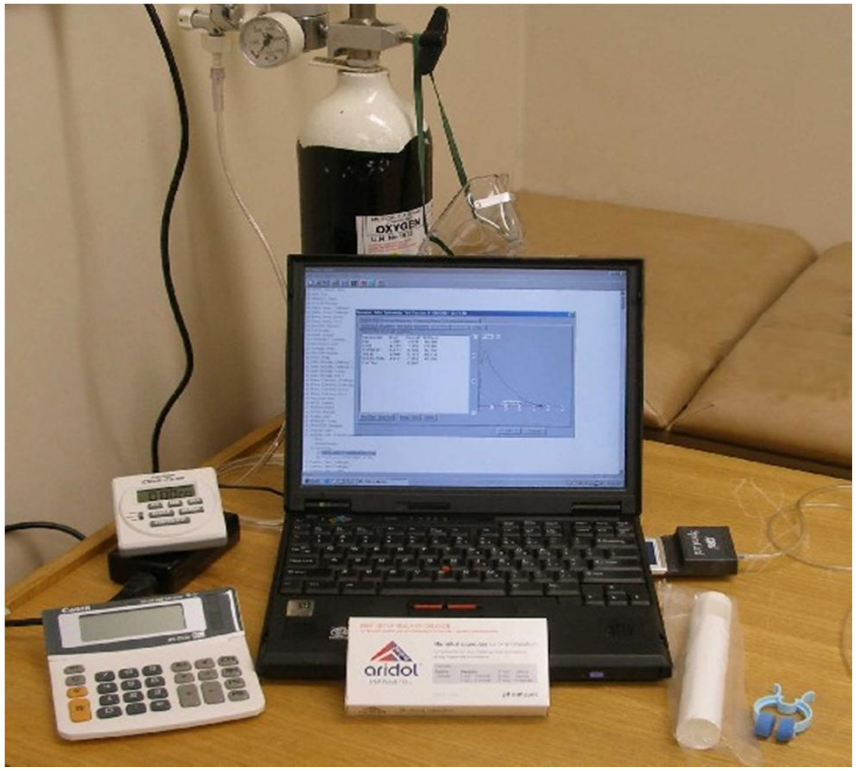
- Is a negative methacholine test result still valid as a rule out test ?

Is Mannitol a Rule in test ?

- In contrast to methacholine, the challenges that act indirectly, via release of mediators such as exercise or mannitol, are promoted as tests that confirm the diagnosis of asthma if the test result is positive but do not rule out asthma if the test result is negative.

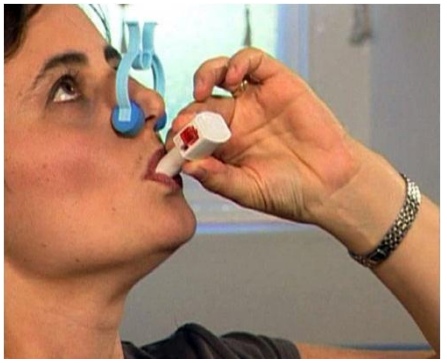
- Is it valid to consider mannitol as a rule in test for asthma and if so, what is the significance of a negative test result?

What equipment is required for a Mannitol Test ?



Equipment

- Aridol™ Kit (containing Aridol™ capsules, inhaler device and instruction leaflet)
- Spirometer & mouthpiece
- Nose clip
- Timer (which can be set to 60 seconds)
- Calculator
- Bronchodilator (eg albuterol) & volumatic spacer (if using a metered dose inhaler)
- Oxygen and other relevant emergency equipment should be readily available as per standard Bronchial Provocation Testing protocols.



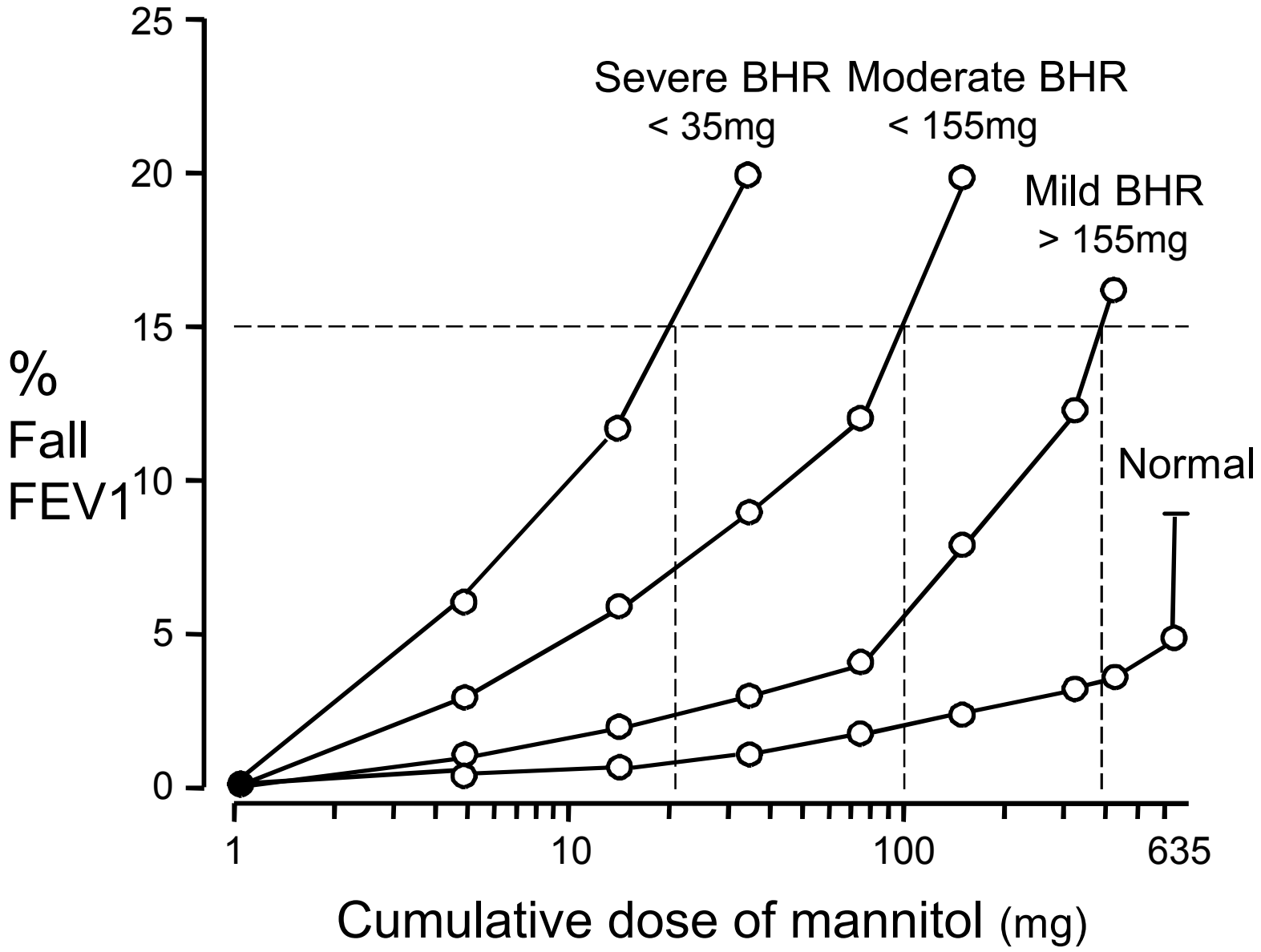
www.mannitoltest.info

What is the protocol used for mannitol and how are the results expressed?

Inhaled agent:	**Dry powder Mannitol**
Progressive Protocol:	**0, 5, 10, 20, 40, 80, 160, 160, 160 mg**
Measurements :	**FEV_1 Pre & 1 min post dose with highest value for FEV_1 recorded**
Positive Response:	**Fall FEV_1 ≥15% or**
	Fall FEV_1 ≥10% between consecutive doses
Expression of result:	
Sensitivity	**PD_{15}**
Reactivity	**Response Dose Ratio**
	Final % fall FEV_1 / Cumulative dose
Recovery:	**Bronchodilator or spontaneous**

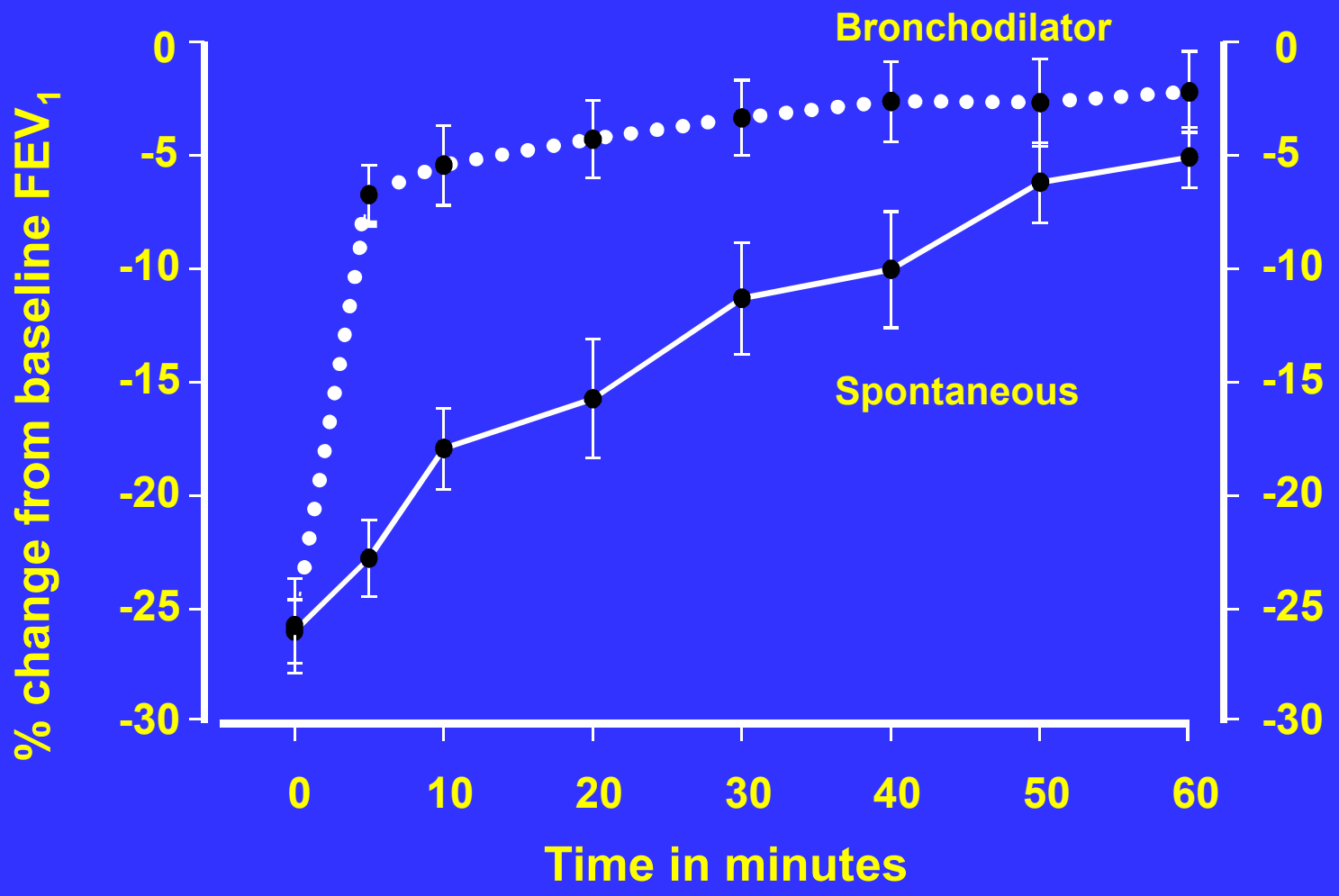
Anderson SD et al AJRCCM 1997;156:758-765,
Brannan JD Anderson SD et al Respiratory Research 2005; Dec PHASE 3 trial
Anderson SD et al Respiratory Research 2009 ; January PHASE 3 trial
Sverrild A et al J Allergy Clin Immunol 2009; 24:928-932

Levels of Bronchial hyperresponsiveness to mannitol



Brannan JD Anderson SD et al Clin Resp J 2007; 1:1-12

Recovery can be Spontaneous or with Bronchodilator Recovery after Dry Mannitol Challenge



Anderson SD et al, 1997; AJRCCM 156:758-65

Q; What Population Studies have been performed using mannitol and methacholine ?

- A301 was the 1st Phase 3 study using mannitol as a BPT. It was carried out in well defined groups including 492 asthmatic and healthy subjects both adults and children. (Brannan JD et al Resp Res 2005;6:144)

- A305 was the 2nd Phase 3 study using both mannitol and methacholine and exercise. It was in a group of 275 subjects with symptoms of asthma who entered the study without a definite diagnosis of asthma (Anderson SD et al Respir Res 2009: 10:4)

- Copenhagen Study comprised an unselected sample of 238 young adults and mannitol and methacholine was used to identify those with respiratory physician diagnosed asthma (Sverrild A et al J Allergy Clin Immunol 2010;124:928)

- Athlete Study: 58 young elite skiers with asthma like symptoms had provocation tests using mannitol, methacholine and dry air hyperpnea (Sue-Chu M et al Brit J Sports Med 2010;44:827)

A 301

Study in well defined populations of asthmatic and healthy subjects

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The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline

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Brannan JD Anderson SD et al Respiratory Research 2005; 6:144

http:respiratory-research.com/articles/browse.asp

A301 Phase 3 trial Per Protocol – Patients' characteristics

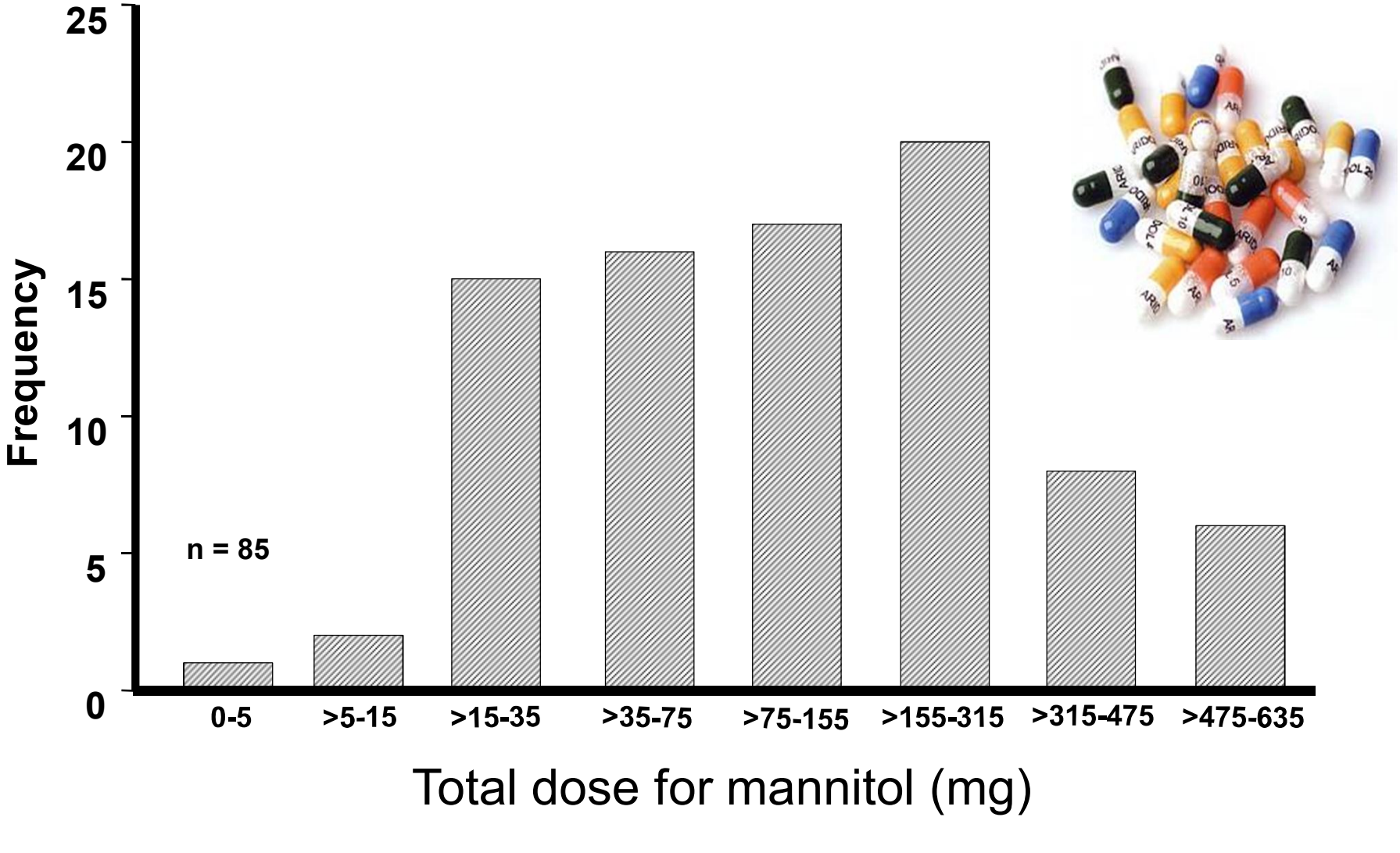
- 592 subjects (466 adults, 126 children) included 487 (82.3%) asthmatics and 105 non asthmatics.
- Age 6 – 83 mean 34.8 yr
- Majority had mild disease
  - Half the asthmatic cohort had infrequent symptoms
  - ***Only 11.3% reported symptoms interfering with normal activity.***
- Majority had good lung function.
  - 50% of the asthmatics had a FEV1 > 95% of predicted.
  - The mean FEV_1 was 3.0 L in the asthmatics and 3.2 L in the non-asthmatics.
- 78.4% taking at least one medication.
  - 228 on combination therapy / 164 on monotherapy with ICS

Brannan JD et al. Respir Res 2005;6:144

ATS 2005 ADULTS	*Mild (n=78)*	*Moderate (n=100)*	*Severe (n=31)*
GeoMean PD_{15} (95%CI)	185 (147, 233)	97 (77, 123)	84 (54, 129)
CHILDREN	*Infrequent Episodic (n=17)*	*Frequent Episodic (n=12)*	*Persistent (n=53)*
GeoMean PD_{15} (95%CI)	144 (92, 223)	120 (69, 208)	73 (50,108)

Cumulative doses of mannitol to cause PD_{15}

60% children responded in ≤155 mg or 6 capsules
83.5% children responded in ≤315 mg or 10 capsules



A 301

"Gold Standard" Clinicians Diagnosis		Clin Dx	Clin Dx Adjusted For ICS
Mannitol n = 492	Sensitivity Specificity	59.8 94.5	
Mannitol n =333	Sensitivity Specificity		89.0 95.0

Sensitivity increased from 60 to 89% when the data were adjusted for the confounding effect of benefit from treatment with inhaled corticosteroids (ICS) and mannitol negative subjects taking ICS were removed.
Age 6 - 83 yrs (Mean 34.8 yr)

Brannan JD Anderson SD et al 2005 Respiratory Research 6: 144

What did we learn from A301 ?

- Mannitol had a high specificity and there were very few false positive tests in the healthy population.

- The sensitivity for mannitol to identify clinically recognised asthma improved from 60 to 89% when the benefit of current treatment with inhaled corticosteroids was taken into account.

COPENHAGEN STUDY was in 14-24 yr olds in a general population with asthmatics identified by a respiratory physician

Original article

Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide: A random-sample population study

Asger Sverrild, MD, Celeste Porsbjerg, MD, PhD, Simon Francis Thomsen, MD, PhD, and Vibeke Backer, MD, DMSc *Copenhagen, Denmark*

Background: Studies of selected patient groups have shown that airway hyperresponsiveness (AHR) to mannitol is more specific than methacholine for the diagnosis of asthma, as well as more closely associated with markers of airway inflammation in asthma.
Objective: We sought to compare AHR to mannitol and methacholine and exhaled nitric oxide (eNO) levels in a nonselected population sample.
Methods: In 238 young adults randomly drawn from the nationwide civil registration list in Copenhagen, Denmark,

Abbreviations used
AHR: Airway hyperresponsiveness
BPT: Bronchial provocation test
eNO: Exhaled nitric oxide
IQR: Interquartile range
RDR: Response-dose ratio
ROC: Receiver operating characteristic

Sverrild A et al, J Allergy Clin Immunol 2009;124:928-32

COPENHAGEN STUDY Subject Characteristics

Sverrild A et al, J Allergy Clin Immunol 2009;124:928-32

TABLE I. Baseline characteristics

	Current asthma (n = 51)	No asthma (n = 187)	*P* value
Age (y), (median [minimum-maximum])	18 (15-24)	19 (14-24)	.77
Sex (% female)	61% (31)	60% (113)	.87
Atopy	77% (39)	32% (60)	<.0001
Smoking (current)	29%	24%	.32
FEV_1% predicted, mean (95% CI)	92% (89% to 95%)	94% (92% to 95%)	.32
FEV_1/FVC ratio, mean (95% CI)	0.85 (0.82-0.87)	0.88 (0.87-0.89)	.001
Use of ICS	16%	0%	<.0001

FVC, Forced vital capacity; *ICS*, inhaled corticosteroid.

One respiratory physician only made the diagnosis based on symptoms in last 1yr, in combination with an FeNO >30 ppb, a history of allergic rhino-conjunctivitis, dermatitis, a positive skin test response, a familial predisposition to atopic disease, non-allergic rhino-conjunctivitis or an FEV_1 /FVC ratio <75%.

COPENHAGEN STUDY

TABLE II. Results of 238 randomly selected adolescents tested with inhaled mannitol and methacholine: 51 asthmatic subjects and 187 nonasthmatic subjects

		Asthma (n=51)		No asthma (n=187)	
		Methacholine		Methacholine	
		+	-	+	-
Mannitol	+	26	4	2	1
	-	9	12	35	149

TABLE III. Diagnostic properties of inhaled mannitol and methacholine in 238 randomly selected subjects

	Sensitivity	Specificity	PPV	NPV
Methacholine	69 (57-78)	80 (77-83)	49 (40-56)	90 (87-93)
Mannitol	59 (51-63)	98 (96-99)	91 (78-97)	90 (88-91)

Sverrild A et al, J Allergy Clin Immunol 2009;124:928-32

What did we learn from the Copenhagen study ?

- Mannitol PD_{15} had a high specificity (98%) compared with methacholine PC_{20} 80% (e.g. there were more false positive tests in non-asthmatics using methacholine than there were using mannitol)

- The sensitivity of mannitol PD_{15} to identify those with clinically recognised asthma was lower than methacholine (59% vs 69%) although small improvements may have occurred when adjusting for treatment.

A 305 was a population of subjects with symptoms but without a definite diagnosis of asthma at study entry

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Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma

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Anderson SD, Charlton B et al Respiratory Research 2009; 10:4
http:respiratory-research.com/articles/browse.asp

A305 Rationale

- No previous large study has reported the utility of bronchial provocation testing in patients without a clear diagnosis of asthma
- Mannitol is a bronchial provocation test approved in the USA

Patient demographics (enrolled subjects)

Age	• Mean (SD) = 24.9 (10.6) yrs • range = 6 – 50 yrs
BMI	• Mean (SD) = 24.5 (4.7) • Range = 14.4 – 39.9
Gender	• 46.4% male • 53.6% female
Ethnicity	• Caucasian – 74% • Black – 9% • Other – 2% Hispanic – 9% Asian – 5%

Patient characteristics at baseline (enrolled)

FEV_1	• Mean (SD) = 91 (8.7)% of predicted at baseline
Atopy	• 78% of subjects
β_2 reversibility	• 10.8% of all screened subjects • 7.5% of PP subjects reversed
NAEPPII asthma severity rating	• Mean (SD) = 1.2 (0.6)* • * 92.2% graded at Step 1 or 2 by clinician at Visit 1, on scale 0 - 4

This was a group of patients with normal spirometry, mild symptoms with an unclear diagnosis

NAEPPII Asthma Severity Grading ?

From Guidelines for Dx and Mx of Asthma NIH 1997 NHLBI

94.2% of 375 subjects graded at Step 1 or 2 at visit 1

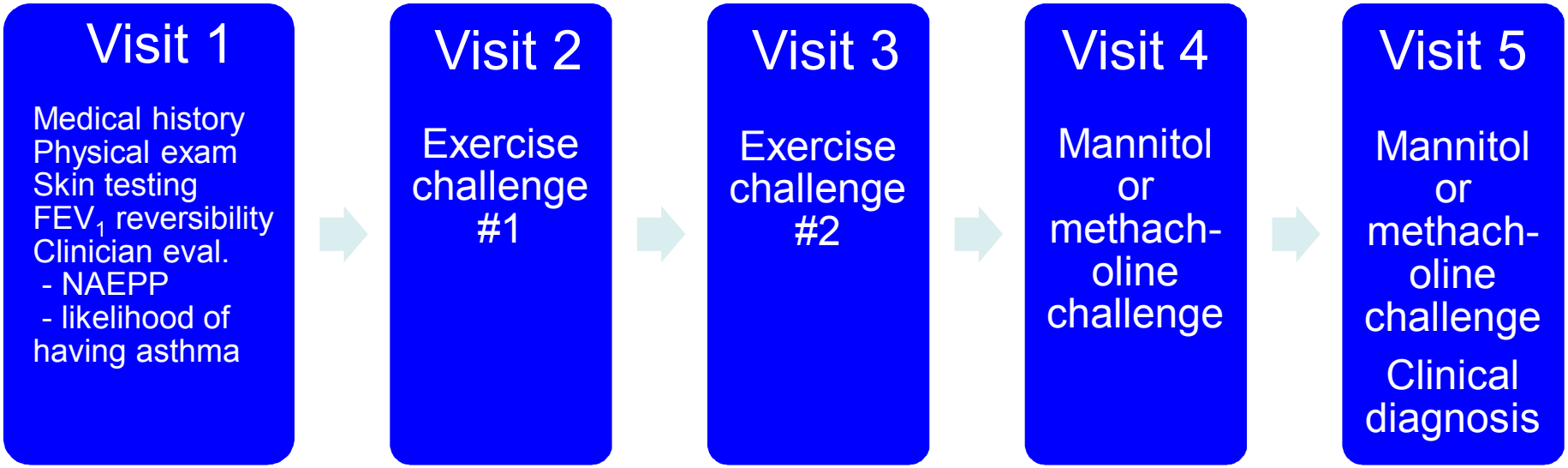
0= None 1.3% 1= Mild intermittent 81.6%, 2= Mild Persistent 12. 6%,
3= Moderate persistent 4.6 %, 4=Severe persistent 0%

STEP 2 Mild Persistent	▪ Symptoms ≥ 2 times a week but < 1 time a day ▪ Exacerbations may affect activity	> 2 times a month	▪ FEV_1 or PEF ≥ 80% predicted ▪ PEF variability 20 – 30%
STEP 1 Mild Intermittent	▪ Symptoms ≤ 2 times a week ▪ Asymptomatic and normal PEF between exacerbations ▪ Exacerbations brief (from a few hours to a few days); intensity may vary	≤ 2 times a month	▪ FEV_1 or PEF ≥ 80% predicted ▪ PEF variability < 20%

A305

*

A305 □ Study Design



Randomization

- All visits separated from next visit by ~ 1 □ 4 days
- Order for mannitol and methacholine challenges was randomized within the exercise negative and exercise positives arms

Blinding

- Mannitol and methacholine challenges performed by staff different from those performing the rest of the procedures
- There was no access to results across groups
- Clinician doing diagnosis at Visit 5 had access to all data except mannitol and the methacholine challenge results

Methacholine and mannitol were equally sensitive for identifying bronchial hyperresponsiveness in the population

- **Methacholine** (5 breath dosimeter method)
  $PC_{20} \leq 16$ mg/ml (fall in FEV_1 of 20% from baseline)
  n= 156 were positive

- **Mannitol**
  $PD_{15} \leq 635$ mg (fall in FEV_1 of 15% from baseline) (or subject experienced a 10% between dose fall in FEV_1)
- 168 were positive

- **Exercise** (8 minute treadmill challenge)
  FEV_1 fall $\geq 10\%$ from baseline on at least 1 of 2 exercise tests
- n=163 were positive

Percentiles and Geometric mean values for bronchial provocation tests and the maximum% fall in FEV_1 recorded after the two exercise tests

	Percentiles			
	25th	50th	75th	Geomean (95% CI)
Mann+ PD_{15} (mg)	72	234	374	158 (129,193)
Mech+ PC_{20} (mg/ml)	0.84	2.98	6.53	2.12 (1.7,2.64)
Exc+ % Fall	23.6%	15.5%	12.4%	19.1% (9.25)*

*Mean (SD)

There was 69% concordance in the mannitol and methacholine results

Methacholine was not more sensitive than mannitol for identifying a clinical diagnosis of asthma at study-end and was less specific than mannitol in children

"Gold Standard"		Whole Group Clin Dx 5+ N = 375	Children<18yr Clin Dx 5+ n=115
Mannitol	**Sensitivity**	**56%**	**63.2%**
	Specificity	**73%**	**81.4%**
Methacholine 16 mg/ml			
	Sensitivity	**51%**	**66.2%**
	Specificity	**75%**	**62.9%**

Clinical diagnosis (Clin Dx) of asthma at Visit 5 made on history, examination, FEV1 reversibility, exercise challenge results, skin tests and questionnaire but NOT the mannitol and methacholine test results.

Anderson SD et al Respiratory Research 2009, 10:4

Methacholine was less sensitive than mannitol for a clinical diagnosis of asthma at NAEPPII Grade 2

PP population

methacholine PC_{20} 16 mg/mL

	Agent	NAEPPII step 1 n= 305	NAEPPII step 2 n =47
Sensitivity	mannitol	0.56	0.75
	methacholine	0.55	0.62

A 305 Mannitol was not more sensitive than methacholine in identifying EIB

"Gold Standard"		Whole Group Clin Dx 5+ N = 375	Whole Group EIB+ 10% N= 375
Mannitol	**Sensitivity**	**56% 73%****	58%
	Specificity	**73%**	**64%**
Methacholine 16 mg/ml			
	Sensitivity	**51% 72%****	**53%**
	Specificity	**75%**	**69%**

Clinical diagnosis (Clin Dx) of asthma at the end of the study was made on history, examination, FEV_1 reversibility, exercise challenge results, skin tests and questionnaire but NOT the mannitol and methacholine test results

** When both exercise tests □10% fall in FEV_1

Anderson SD et al Respiratory Research 2009, 10:4

A 305

Sensitivity of mannitol was improved when those with a prolonged challenge time were excluded

Exercise Positive Cut-Points - % fall from baseline		10%	15%	20%
Mannitol	Sensitivity	58.6	69.4	78.6
n = 372	Specificity	65.2	62.0	60.8
Excluding those with challenge >35 min		64.1	75.3	82.7
	Sensitivity	59.9	57.0	55.4
n = 319	Specificity			
Methacholine 16 mg/ml	Sensitivity	55.2	67.4	80.3
n = 375	Specificity	68.9	66.1	65.2

There was a high rate of negative methacholine tests in those given a clinical diagnosis of asthma

If methacholine negative had been adhered in order to rule out a diagnosis of asthma then:
118 (49%) fewer subjects would have been diagnosed

	Clin Dx +ve n=240	Clin Dx –ve n= 135
Methacholine +ve	122 GM 2.14 mg/ml	34 2.04 mg/ml
Methacholine -ve	118 > 16 mg/ml	101 > 16 mg/ml

Diagnosis by a Respiratory Physician on basis of comprehensive information only such as History,Examination,FEV_1Reversibilty two exercise tests, Skin tests and Questionnaires

Anderson SD et al Respir Res 2009:

What did we learn about methacholine from A 305 ?

- That Methacholine was no more sensitive for identifying BHR than mannitol or exercise and no more sensitive than mannitol for identifying a clinical diagnosis of asthma.

- There was a high rate of methacholine negative test results (49%) in those given a clinical diagnosis of asthma by a respiratory physician at the end of the study

- based on comprehensive information that included History FEV_1 reversibility, two exercise tests,skin tests, questionnaire (the results of the methacholine or mannitol test results were withheld) suggests that:

- a negative methacholine test result should not be relied upon to rule out a diagnosis of asthma in subjects with symptoms of asthma but without a definite diagnosis.

- The importance of these observations is that it is subjects with these characteristics who are most likely to be referred for testing.

When put to the rule out test ?

- The long-held belief that the clinical utility of methacholine is in a negative test result excluding a diagnosis of asthma was not upheld when the respiratory physician did not have access to the methacholine test result.
- ***54% (118) of all those negative to methacholine were given an asthma diagnosis at Visit 5 on the basis of other information.***
- ***Would the Doctors have reversed their decision had they known the methacholine test was negative?***
- If a methacholine negative test had been used to Rule out Asthma then 73 subjects with EIB (mean % fall FEV_1 of 15.6%) and 63 subjects positive to mannitol would have been missed.

*

What did we learn about Mannitol as a rule in test ?

- Mannitol was as sensitive as methacholine for identifying BHR.
- Mannitol was never less sensitive than methacholine to identify a clinical Dx of asthma when cut points of 8, 12 or 16 mg/ml were used.
- The concept that mannitol would identify all those with EIB was not supported by A305 with 42% of those with EIB on 1 of 2 tests being mannitol negative whilst 28% of those with 2 positive tests were missed.
- The clinical utility of mannitol positive test result was upheld by the low number of false positive tests in A301 and Copenhagen studies & the ***high concordance (78.5%) between a clinical Dx at Visit 5 & a positive mannitol in A305.***

If mannitol positive had been adhered to in order to rule in a diagnosis of asthma then 36 more subjects would have been diagnosed

	Clin Dx +ve n=240	Clin Dx –ve n=135
Mannitol +ve	134	36
Mannitol -ve	106	99

Diagnosis by a Respiratory Physician on basis of History,Examination, FEV_1Reversibilty 2 exercise tests, Skin tests Questionnaires

Anderson SD et al Respir Res 2009:

Mannitol positive subjects compared with mannitol negative subjects

- In mannitol +ve subjects a PC_{20} Methacholine is more frequent (66% vs 25%) and the PC_{20} significantly lower 1.64 vs 3.54 mg/ml $p<0.001$ (Anderson SD et al Respir Res 2009)

- In mannitol +ve subjects EIB is more common (57% vs 33%) and more severe 21±10% vs 16±7% $p<0.001$) (Anderson SD et al Respir Res 2009;10:4)

- In mannitol +ve subjects FeNO is significantly higher 47 vs 19 ppb (Sverrild S et al JACI 2010)

- In those with eosinophilic asthma 82% are +ve to mannitol (Porsbjerg et al J Asthma 2009;46)

Summary Rule in Rule out:

- The profile of those with a positive mannitol test result was consistent with ruling in a diagnosis of asthma in that there was a low rate of false positive tests in A301 and Copenhagen Study and 78% of subjects in A305 were given the diagnosis of asthma by a respiratory physician. In all studies the physician was blinded to the mannitol test result.

- The profile of those with a negative methacholine test result was less consistent with ruling out a diagnosis of asthma in that 49% of subjects in A305 were given the diagnosis of asthma by a respiratory physician when they were blinded to the methacholine test result.

*What about the subjects **without** a Clinical Diagnosis at Visit 5 ?*

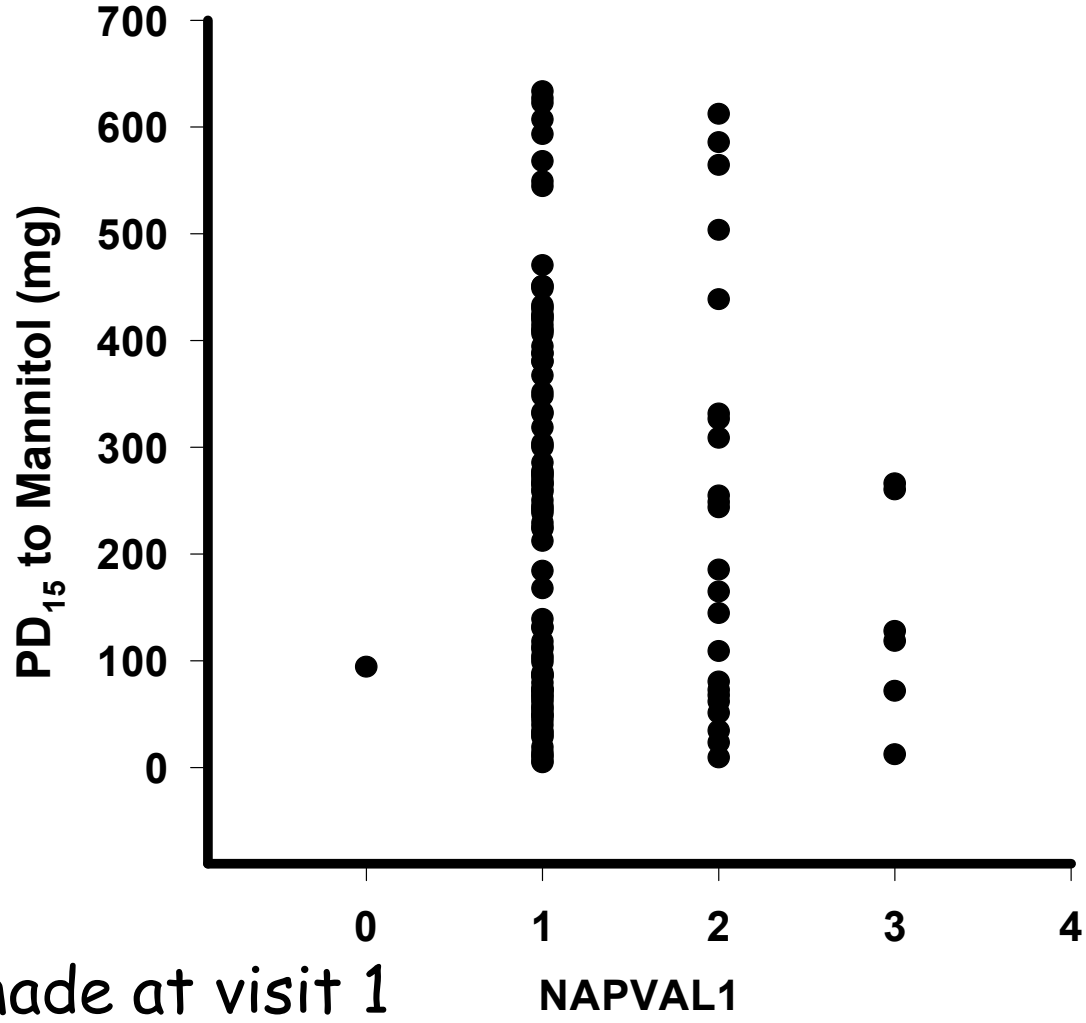
n= 135

- ***25% were positive to mannitol***
- ***9% had EIB >10% fall in FEV_1 Mean fall 13% ± 3***
- ***1.0% had EIB with 2 tests >10% fall***
- 22% positive to methacholine ≤16 mg/ml
- *8% were positive to methacholine and mannitol*
- ***2% positive to mannitol and exercise***
- *1% were positive to exercise & mannitol & methacholine*

NB clinician giving the diagnosis of asthma had Hx, Qx, reversibility, skin tests and exercise results ONLY

*

Mannitol Responsiveness occurred at all NAEPPII Steps of Asthma Severity



Grading made at visit 1

0= None 1.3%1= Mild intermittent 81.6%, 2= Mild Persistent 12. 6%, 3= Moderate persistent 4.6 %, 4=Severe persistent 0% n = 375 P Males 182 Females 193

A305

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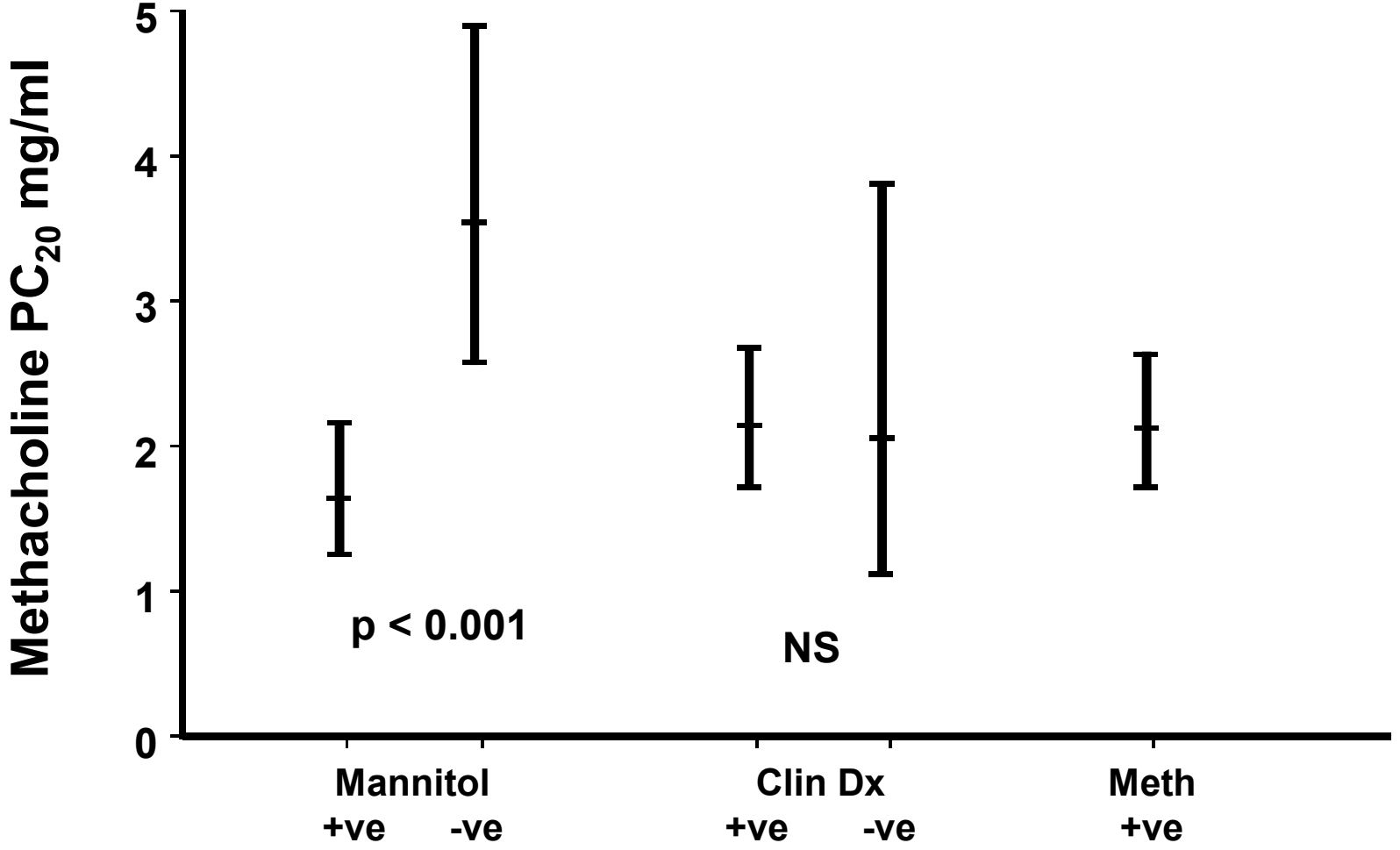
In subjects negative to mannitol, BHR to methacholine was less common & PC_{20} was significantly higher compared with mannitol positive subjects. This difference in PC20 is not evident for a positive or negative clinical diagnosis



	Mannitol +ve	Mannitol -ve	Clin Dx +ve	Clin Dx -ve	Meth +ve
% of subjects +ve methacholine	62%	25%	51%	25%	100%

Mannitol positive test associated with significantly higher FeNO compared with mannitol negative test

	Current asthma (n = 51)			
	Mannitol		Methacholine	
	Negative (n = 21)	Positive (n = 30)	Negative (n = 16)	Positive (n = 35)
eNO (ppb), median (IQR)	19 (13-30)	47 (35-62)	24 (15-39)	37 (26-51)
P value	.001		.13	
eNO >26 ppb, %(n)	29 (6)	70 (21)	44 (7)	57 (20)
P value	<.0001		.07	

	No asthma (n = 187)			
	Mannitol		Methacholine	
	Negative (n = 184)	Positive (n = 3)	Negative (n = 150)	Positive (n = 37)
eNO (ppb), median (IQR)	14 (13-15)	46 (10-214)	13 (12-41)	17 (13-21)
P value	<.0001		.03	
eNO >26 ppb, %(n)	11 (21)	100 (3)	11 (16)	22 (8)
P value	.01		.07	

Sverrild A et al JACI 2010

AHR, FeNO & inflammatory phenotype

Eosinophilic phenotype have greater AHR and higher FeNO compared to neutrophilic

	Eosinophilic		Non-eosinophilic		
	Eosinophilic asthma (n=27)	Mixed granulocytic asthma (n=8)	Neutrophilic asthma (n=8)	Pauci-granulocytic asthma (n=19)	p
AHR to mannitol	82%	75%	50%	58%	0.20
PD_{15}(mg) (median (IQR))	107 mg §□ (185mg)	186mg (379mg)	512mg (294mg)	238mg (391mg)	0.02
eNO (ppb) (median (IQR))	77ppb §□ (86ppb)	47ppb§§ (79ppb)	12ppb □□ (22ppb)	48ppb (44ppb)	0.001

Porsbjerg C, *et al.* J Asthma 2009; 46:606-612

So what does BHR to mannitol indicate?

- That there are a sufficient number of cells with a sufficient concentration of mediators
- AND a responsive bronchial smooth muscle to those endogenously released mediators at the time of testing
- Likely but not necessarily to have
- Exercise induced bronchoconstriction
- eosinophils in sputum
- high FeNO
- Positive methacholine test
- And will respond to inhaled steroids and other drugs used in treatment of asthma

Are we over diagnosing asthma in elite athletes using methacholine?

What about methacholine as Rule in test?

- Many clinicians use a positive methacholine test result as diagnostic of asthma at a PC_{20} <16 mg/ml.

- Many factors however can contribute to BHR to methacholine.

- BHR at PC_{20} <16 mg/ml can reflect airway injury from breathing large volumes of unconditioned air (e.g. cross country skiers or skaters) cigarette smoking or inhalation of pollutants (e.g. swimmers) or remodelling of the airways in response to childhood asthma.

- The findings of positive methacholine responses in elite athletes both with and without symptoms of asthma suggest that we should question if a positive methacholine test result is always consistent with a diagnosis of asthma .

Athlete Study

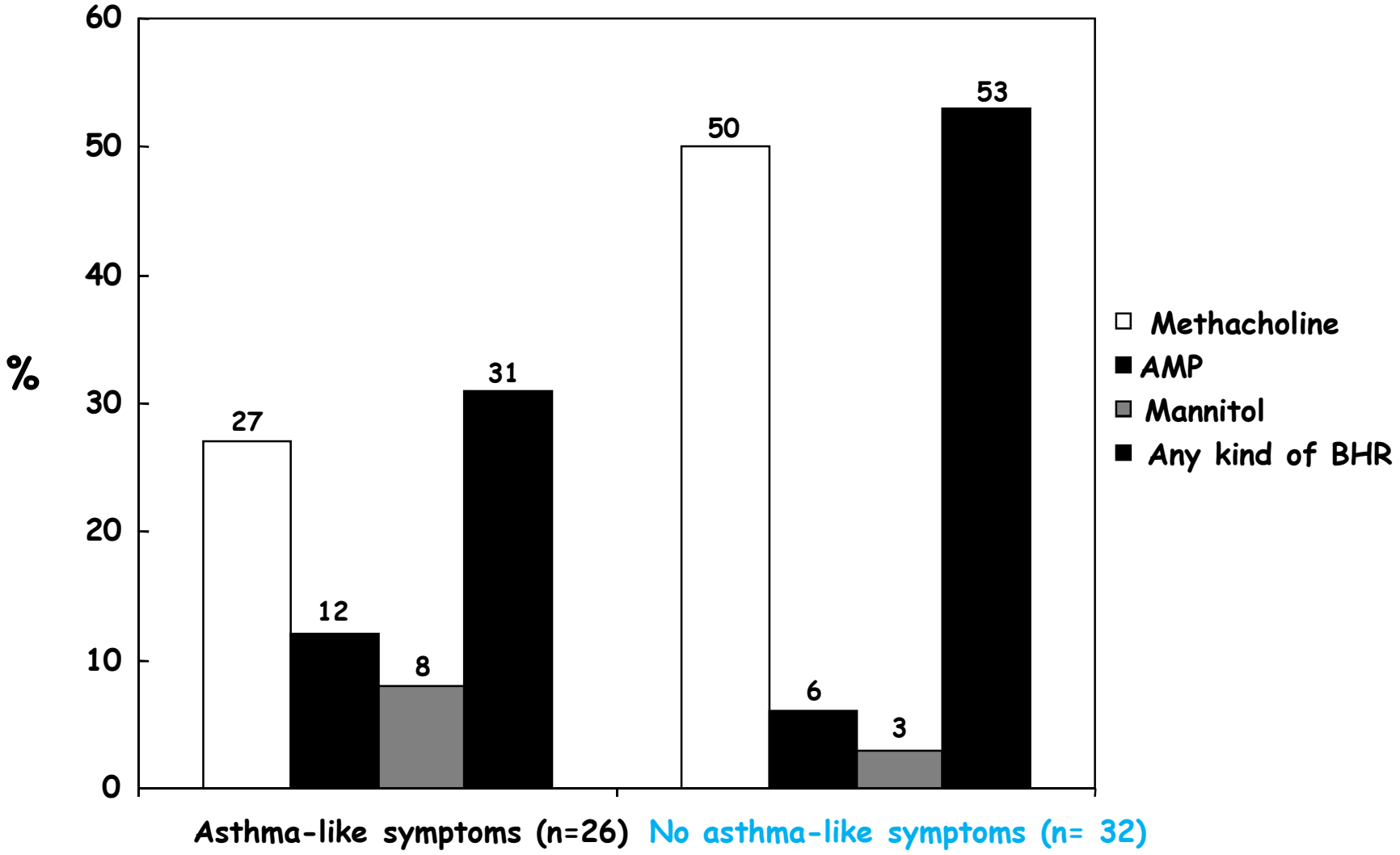
Original article

Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers

Malcolm Sue-Chu,[1,2] John D Brannan,[3] Sandra D Anderson,[3] Nora Chew,[4] Leif Bjermer[5]

Methods Exhaled nitric oxide concentration (F_ENO), spirometry and bronchial challenge in random order with methacholine, AMP and mannitol were consecutively performed on three study days in the autumn. Specific IgE to eight aeroallergens and a self-completed questionnaire about respiratory symptoms, allergy and asthmatic medication were also performed on day 1. Eucapnic voluntary hyperventilation (EVH) and field exercise tests were randomly performed in 33 of the skiers on two study days in the following winter.

High Prevalence of airway hyperresponsiveness to methacholine, and low prevalence of response to AMP and Mannitol in Young skiers with and without symptoms of asthma.



Sue Chu et al Brit J Sports Med 2010

Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers

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Conclusions Methacholine hyperresponsiveness is more common in asymptomatic skiers and is a poor predictor of hyperresponsiveness to mannitol and hyperpnoea. The low prevalence of hyperresponsiveness to indirect stimuli may suggest differences in the pathogenesis of methacholine hyperresponsiveness in elite skiers and non-athletes.

A positive methacholine test in an athlete may indicate airway injury rather than asthma

Thus methacholine is not a useful rule in test in athletes

Why challenge with Mannitol?

Advantages :

- Dose-response curve obtained
- Median time taken for $+^{ve}$ test 17 min, $-^{ve}$ test 26 min
- More than one mediator involved PGD_2 LT's, Hist
- Predicts potential for exercise-induced asthma
- Negative test in asthmatic = good control of asthma
- Response dose ratio guide to back titration of steroid
- Positive test = currently active airway inflammation
- Identifies those who would benefit from Rx with ICS

Disadvantage :

- Some cough during challenge